The Role of Exercise and Rehabilitation in the Prevention and Treatment of Breast Cancer related to Lymphedema, Function, and Quality of Life

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Learning Objectives

• Describe physiological mechanisms leading to lymphedema in breast cancer survivors, including treatment modalities that can increase lymphedema risk.

• Describe breast and arm lymphedema in breast cancer survivors, recognize signs and symptoms, and be knowledgeable about treating or referring for those conditions.

• Describe the role of exercise and complete decongestive therapy (CDT) in the prevention and treatment of lymphedema, as well as additional benefits of exercise in breast cancer survivors.

• Describe the role of prehabilitation in improving health outcomes in breast cancer survivors, as well as the role of rehabilitation in lowering the risk of breast cancer recurrence.

Focus on Breast Cancer Survivors

• “One who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease. In cancer, a person is considered to be a survivor from the time of diagnosis until the end of life.” - National Cancer Institute

Learning Objective #1

Describe physiological mechanisms leading to lymphedema in breast cancer survivors, including treatment modalities that can increase lymphedema risk.

Anatomy and Physiology of the Lymphatic System

• Network of lymph, lymph vessels, lymph nodes, and lymphatic organs
  • One-way transport system for fluid, proteins, and other substances
  • Collect fluid from the interstitium and return to the bloodstream

• Major functions
  • Regulation of tissue fluid balance
  • Transport route for immune cells, tumor cells, hormones, nutrients, waste products, proteins, and other molecules
  • Lipid absorption and transport from the gastric system
  • Removal of cellular debris
  • Reservoir for proliferating white blood cells and tumor cells (lymph nodes)

Lymphatic System Structures and Components

• Lymph
• Lymph vessels
• Lymph nodes
• Lymphatic organs/tissues (e.g. spleen, thymus, tonsils & adenoid, bone marrow)
Lymph

- Fluid that travels throughout the body via a network of lymphatic vessels
- Forms when interstitial fluid moves into lymphatic capillaries
- Composed of 96% water and 4% solutes
  - Various proteins, lipids, glucose, urea, creatinine, amino acids, electrolytes, and lymphocytes

Lymph Vessels

- Transport lymph throughout the body
- Lymphatic capillaries: small, closed-ended tubes through which fluid from tissues enters the lymphatic system
- Lymphatic vessels: move lymph to and from lymph nodes
  - Pre-nodal vs. post-nodal (afferent vs. efferent)
  - Contain valves which aid in one-way propulsion of lymph
  - Segments of lymphatic vessels between valves form contractile compartments
- Collecting ducts: return lymph to the bloodstream

Lymph Nodes

- Filter and remove harmful substances from lymph before returning it to the bloodstream
- Named according to location
  - Cervical lymph nodes located in neck
  - Thoracic and mediastinal lymph nodes located in chest
  - Axillary lymph nodes located in the armpit
  - Pari-aortic, peri-aortic, and mesenteric lymph nodes located in the abdomen
  - Inguinal lymph nodes located in the groin
- Activate the immune system
  - Lymphocytes and macrophages
- Possible swelling and tenderness when a large number of particles are filtered through a lymph node

Lymphatic Organs/Tissues

- Spleen: largest lymphatic organ; removes worn out red blood cells, lymphocytes, and foreign invaders; stores red blood cells and lymphocytes
- Thymus: site where T lymphocytes mature and multiply
- Tonsils and adenoid: trap bacteria and viruses
- Bone marrow: site of hematopoiesis
  - Red blood cells: transport of respiratory gases
  - White blood cells: immune system cellular components
  - Platelets: blood clotting

Formation of Lymph

Blood hydrostatic pressure drives net filtration
- Interstitial fluid osmotic pressure
- Blood colloid osmotic pressure

Blood hydrostatic pressure drives net reabsorption
- Interstitial fluid hydrostatic pressure
Transport of Lymph

- No pumping organ
- Mechanisms that facilitate transport of lymph
  - Valves to prevent backflow
  - Smooth muscle contractions in the lymphatic vessel walls
  - Intrathoracic pressure changes during breathing
  - Pulscations of nearby arteries
  - Skeletal muscle contractions
  - Movement of adjacent tissue

Lymphedema

- Progressive swelling that occurs when protein-rich fluid accumulates in the interstitium
- Primary lymphedema
  - Genetic and familial abnormalities in lymphatic structures or function
- Secondary (acquired) lymphedema
  - Secondary to damage of lymphatic structures

Physiological Mechanisms Leading to Lymphedema

- Variations in capillary and interstitial pressures
- Alterations in lymph transport mechanisms and/or lymphatic structures
  - Fibrosis that impedes muscle movement
  - Fibrotic lymph nodes
  - Removal of lymph nodes and vessels

Surgery and Lymphedema

- Involves removal of tumor, lymph nodes, lymph vessels, and surrounding tissues
- Common terms related to breast cancer surgery
  - Lumpectomy: removes tumor and adjacent tissue from the breast; aka breast conserving surgery
  - Mastectomy: removes all breast tissue
  - Sentinel node biopsy (SLN): removes fewer nodes (i.e., 1-7 nodes)
  - Axillary lymph node dissection (ALND): removes larger number of nodes (i.e., >7 nodes)
- Alters normal anatomical structures, creates scarring
  - Disrupts lymphatic transport

Radiation Therapy and Lymphedema

- Involves delivering high energy radiation to structures in order to kill cancer cells
  - For breast cancer, often consider radiation to the axilla, breast, or chest
- Creates scarring, fibrosis of lymph nodes and other lymphatic structures, tissue injury due to inflammatory responses
  - Obstructs lymphatic drainage
  - Damages lumens of lymphatic trunks
  - Alters cell membranes of lymphatic vessels
  - Disrupts lymphatic transport

Surgery, Radiation Therapy, and Lymphedema Risk

- Most women developing breast cancer related lymphedema (BCRL) will do so within 3 years of diagnosis
- 5-year cumulative incidence of BCRL is 42%
  - 80% develop BCRL within 2 years
  - 89% develop BCRL within 3 years
- BCRL risk factors appear to be additive
- Other factors that can increase BCRL
  - Increased BMI
  - Infection post-surgery
Chemotherapy and Lymphedema

- Involves administering systemic therapy in order to kill cancer cells
- For breast cancer, taxane chemotherapy (particularly docetaxel) associated with increased peripheral fluid retention
  - Increased capillary permeability and filtration of plasma proteins
  - May place added stress on lymphatics in the arm on the side of surgery

Does docetaxel lead to lymphedema?

- Can lead to an increase in extracellular fluid, which can present as fluid retention in the extremities
- Patients may experience mild swelling, but may not necessarily experience subsequent lymphedema
- Peripheral fluid retention tends to be more global in nature and tends to resolve

Relationship between docetaxel and upper limb lymphedema is unclear

- Adjust for other factors that are known to increase lymphedema risk (e.g., axillary lymph node dissection)

Clinical importance of being able to distinguish between mild or transient edema vs. chronic lymphedema

Take-Aways for Learning Objective #1

- Lymphatic system includes a network of vascular structures, tissues, and organs which drive a multitude of physiological functions
  - Fluid balance within tissues
  - Transport and removal of substances
  - Immune system function

- Formation of lymph occurs when excess interstitial fluid moves into lymphatic capillaries and vessels
  - Blood hydrostatic pressure and blood colloid osmotic pressure drive fluid exchange between tissue capillaries and the interstitium

- Lymphatic transport relies on a variety of local and systemic mechanisms
  - No pumping organ

Lymphedema Revisited

- Abnormal accumulation of protein-rich fluid in one or more body parts

Upper extremity lymphedema

- Typical: Pitting, fibrosis, c/o heaviness, discomfort, typically begins distally
- Atypical: Redness (streaking), proximal sudden onset edema, pain
Lymphedema onset in hand / wrist

Lateral trunk edema s/p mastectomy

Lymphedema

- **Typical**: Orange peel / golf ball appearance, heaviness, fibrosis, distal dependent edema, appears “lifted”
- **Atypical**: Redness, warmth, pain

Complete Decongestive Therapy (CDT)

- Manual Lymph Drainage
- Compression Bandaging
- Remedial Exercise
- Skin Care
- Garments, pumps, etc.
- Important to have treatment provided by CLT
  - [https://www.lymphnet.org/](https://www.lymphnet.org/)
  - [https://www.clt-lana.org/](https://www.clt-lana.org/)
Precautions Related to Treating Individuals with Lymphedema Risk

- No heat in involved quadrant
- No BP/blood taken on involved arm
- No exercise with active infection
- No ultrasound in involved quadrant
  - May consider no ultrasound anywhere
- No highly repetitive arm exercise (UBE) without compression

Precautions Related to Other Medical Conditions

- Congestive heart failure
- Peripheral artery disease
- Kidney failure
- Acute or active infection
- Active blood clots (DVTs)
- Active cancer

Lymphedema Risk Reduction Practices

- Compression sleeve for flying
- Avoiding very hot temps / hot tubs / saunas
- Skin care – sunscreen, insect repellent
- No blood pressure / needle sticks in involved quadrant
- Call MD if there are concerns of infection (redness, warmth, pain, swelling)

Take-Aways for Learning Objective #2

- Lymphedema is an important consideration in anyone with a history of cancer. You need to recognize risk based on history and recognize signs/symptoms to either treat or refer.
- Standard of care in U.S. is CDT – manual lymph drainage, compression bandaging, skin care, and exercise.
- Precautions to consider include comorbidities listed in previous slide that you should discuss with referring MD; also avoid repetitive UE exercise, blood pressure checks on involved arm, hot temp situations, anything that may impact skin integrity.
- When in doubt (infection or recurrence concern), don’t hesitate to contact MD.

Learning Objective #3

Describe the role of exercise and complete decongestive therapy (CDT) in the prevention and treatment of lymphedema, as well as additional benefits of exercise in breast cancer survivors.

Benefits of Exercise in Breast Cancer Survivors

- Can significantly improve physiological, psychological, and functional parameters
  - Examples include cardiorespiratory function, body composition, strength, fatigue, depression, quality of life
- Moderate-to-vigorous intensity progressive exercise improves cancer-free survival and quality of life
- Improves tolerance to subsequent treatments in patients who experience a recurrence
- Reduces risk of other comorbid conditions (e.g., cardiovascular disease, Type II diabetes mellitus, etc.)
Potential Biological Mechanisms

- Likely similar to those proposed for influencing primary risk
  - Modulation of metabolic biomarkers (e.g., decreased glucose and insulin levels, decreased insulin resistance, improved insulin sensitivity)
  - Modulation of sex hormone levels (e.g., estrogen)
  - Improved immune system surveillance
  - Reduced systemic inflammation and oxidative damage

Exercise Programming Recommendations for Breast Cancer Survivors

- **Avoid inactivity**

Aerobic exercise

- 150 minutes at moderate intensity (40-59% of VO₂max; RPE of 12-13), 75 minutes at vigorous intensity (60-85% of VO₂max, RPE of 14-17), or an equivalent combination of the two per week

Resistance exercise

- Begin with low resistance (e.g., < 30% of 1-RM); progress with smallest increments possible
- At least 1 set of 8-12 repetitions, 2-3 days per week
- Free weights, machines, or weight-bearing functional tasks that target all major muscle groups

Some considerations

- Specific exercise prescription requires an individualized approach
- Slower progression of exercise compared to healthy adults, particularly if exercise prescription leads to increased fatigue or other adverse symptoms
- Up to 90% of cancer survivors will experience cancer-related fatigue at some point
- Otherwise, exercise prescription may be the same as for healthy adults
- Can perform several short bouts of exercise per day
- Be aware of increased bone fracture risk and modify exercise prescription accordingly

Some reasons to avoid exercise

- Immediately following surgery
- Severe anemia
- Worsening condition
- Active infection

Role of Exercise in Preventing and Treating Lymphedema in Breast Cancer Survivors

- **Rationale for exercise interventions**
  - Significant risk factors for BCRL include ALND, radiation therapy, and obesity
  - Women with BCRL may experience pain, impaired UE mobility and function, decreased physical activity, fatigue, stress, negatively impacted mental and psychological function, and poorer QoL
  - Functional limitations related to increased pain, decreased strength, and increased edema
  - Early intervention can significantly reduce BCRL during the first year post-treatment

- **Tissue changes associated with BCRL**
  - Increased deposition of fibrosclerotic tissue and fat as lymphedema progresses
  - Altered fat and lean tissue in affected limb compared to non-affected limb
Outcomes of slowly progressive weight lifting in women with BCRL
- Increased upper and lower extremity muscular strength
- Increased shoulder ROM
- Increased lean mass and bone mineral density in affected limb
- Decreased fat mass in affected limb
- Reduced number and severity of BCRL symptoms
- Reduced incidence of BCRL exacerbations

Possible physiological mechanisms
- Increased muscle pump effectiveness
- Improved tissue composition in affected limb
- Lymphedema environment seems to respond favorably to a weight training stimulus
  - Lymphedematous tissue has been shown to have vascular insufficiency, higher adipogenic gene expression, and enhanced ability to undergo adipogenic differentiation, lower vasculogenic gene expression

Outcomes of CDT in women with BCRL
- Significant reductions in arm volume, particularly in women with larger baseline PEV
  - In women with smaller baseline PEV, may not see significant reductions in arm volume, although lymphedema does not appear to progress (over 24 months)
- At the same time, younger age and lower PEV have been correlated with better CDT response
- Reductions in PEV and PREV shown to be ~50%
- 10-12 sessions of CDT
- Majority of lymphedema reduction seems to occur within the first 10 days of CDT
- Improved lymphedema grade
  - Severe improved to moderate
  - Moderate improved to mild
- Improved physical and mental function (SF-36 QoL form)
- Decreased pain, heaviness, and tension
- Increased shoulder ROM
- Effects of CDT can be maintained long-term (24 months)
  - Patient compliance is necessary

Rationale for CDT interventions
- Reduction of edema volume can help improve QoL
- Important to identify predictors associated with lymphedema severity and CDT response

Metrics used to assess CDT effectiveness
- Percentage of excess volume (PEV) = ([volume of affected limb – volume of non-affected limb] / [volume of non-affected limb] * 100)
- More effective measure compared to absolute arm volume
- Removes confounding factors of body shape and body weight
- Percentage reduction in excess volume (PREV) = ([baseline volume of affected limb – posttreatment volume of affected limb] / excess volume) * 100
- PREV = 100% indicates that the volume of the affected limb has been reduced to the volume of the non-affected limb
- Measure of CDT efficacy

Take-Aways for Learning Objective #3
- Effects of exercise in breast cancer survivors mirrors those in healthy and other clinical populations
  - Moderate-to-vigorous intensity progressive exercise improves cancer-free survival and quality of life
  - Improves tolerance to subsequent treatments in patients who experience a recurrence
  - Multiple potential physiological mechanisms
  - Most important exercise recommendation: avoid inactivity
    - Combination of moderate-to-vigorous aerobic exercise most days of the week
    - Slowly progressive resistance exercise 2-3 days per week
    - Regular flexibility exercise can help to address specific areas of joint or muscle restriction that may be related to treatment
    - Recognize that the approach to exercise prescription is individualized
    - Recognize special precautions and contraindications to exercise

Role of exercise in preventing/treating BCRL, particularly slowly progressive weight lifting
- Increased upper and lower extremity muscular strength
- Increased shoulder ROM
- Improved tissue composition, particularly of affected limb
- Reduced number and severity of BCRL symptoms
- Reduced incidence of BCRL exacerbations

Role of CDT in preventing/treating BCRL
- 10-12 sessions shown to reduce PEV and PREV by ~50%
- Age and baseline PEV may be most significant predictors of CDT response
- Improved lymphedema grade
- Improved physical and mental function (SF-36 QoL form)
- Decreased pain, heaviness, and tension
- Increased shoulder ROM
- Effects of CDT can be maintained long-term
  - Patient compliance is an important factor
  - Patients with all grades of lymphedema encouraged to seek out CDT early post-treatment

Describe the role of prehabilitation in improving health outcomes in breast cancer survivors, as well as the role of rehabilitation in lowering the risk of breast cancer recurrence.
**Prehab**

- "The period during which one drinks or does drugs, i.e. before one goes to rehab" – Online Slang Dictionary
- "Prehabilitation is a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments."

**Prehab Considerations**

- Walking Program – 30 minutes daily (at least 5x/week)
- Water walking or recumbent bike if ortho issues
- Exercise classes – strength training, yoga, Zumba, etc
- May improve surgical outcomes / change surgical options
- Potential improved tolerance of chemotherapy
- Give patients sense of control when everything feels out of control

**Baseline Assessment**

- Assessment done after cancer diagnosis before treatment is initiated
- Helps determine lymphedema diagnosis
- Need bilateral measurements due to weight changes
- Helps determine post-operative goals
- Helps us know when a patient comes in with lymphedema concerns if she has measurable difference from baseline

**Baseline Assessments May Include:**

- Shoulder/cervical ROM
- BMI
- Circumferential measurements
- Posture assessment
- Upper extremity strength
- Baseline exercise regimen
- Work duties assessment
- Home situation
- Pain assessment
- Education on importance of exercise program
- Education on post op expectations
- Post op home exercise program
- Lymphedema risk/risk reduction recommendations
- UE functional questionnaire

**Lymphedema Risk Reduction in Breast Cancer Patients: Close Surveillance and the Benefits Related to Functional Outcomes**

- Inclusion: Having SLNB or ALND
- Baseline, post op, 6, 12, 24 month assessments
- Measured circumference of UE, questioned about breast swelling, # nodes removed, DASH (Disabilities of Arm, Shoulder, Hand), shoulder ROM, exercise assessment, weight / BMI, radiation +/- and location, +/- chemo, +/- anti-estrogen therapy

**Preliminary Results**

- 66 patients enrolled, 48 completed
- 15 dropped out (sx elsewhere, too stressed, died, change in medical status, unable to reach pt)
- 3 left to complete
- 11 had signs of breast lymphedema; 7 of those had resolved symptoms by 24 months post op with intervention (CDT or compression bra/pump)
- 6 had signs of UE lymphedema; 4 of those had resolved symptoms by 24 months post op with intervention (CDT or compression garment)
- During study period, 12.5% had some UE lymphedema and 23% had breast swelling
- By 24 months post op, so far...4% have UE lymphedema and 8% have persistent signs of breast lymphedema
Take-Aways for Learning Objective #4

- Prehab can essentially help patients tolerate cancer treatment with greater ease
- Studies show improved overall outcomes with those participating in prehab programs
- Baseline assessments allow for easier lymphedema detection later
- Close surveillance of those at risk for lymphedema for 2 years post op may reduce percent of clinically significant lymphedema

References


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